REMARKS

The present document is submitted in reply to the Office Action dated July 22, 2010 ("current Office Action").

Applicant has amended claim 1 to more distinctly claim the subject matter he deems as his invention. Support for this amendment appears in original claim 2 and the Specification at pages 22-35, Examples 3-8 and 10-13. Applicant has also narrowed claim 2 and added new claims 22 and 23. New claims 22 and 23 are merely two subsets of claim 1. Finally, Applicant has cancelled claim 6. Claim 5 was previously cancelled.

Upon entry of the proposed amendment, claims 1, 4, 11, 14-17, 22, and 23 will be under examination.[1] Note that claims 2, 3, 7-10, 12, 13, and 18-21 have been withdrawn. Applicant respectfully requests that the Examiner reconsider this application in view of the following remarks.

The Examiner rejects claims 1, 11, and 14-17 for obviousness over Samid, US Patent 5,877,213 ("Samid"). See the Office Action, page 3, first paragraph.

Applicant will discuss claim 1 first. Claim 1, as amended, is drawn to a method of using a histone hyperacetylating agent (e.g., phenylbutyrate) to increase therapeutic gain in a subject undergoing chemotherapy (the non-elected species) or radiotherapy (the elected species). In particular, the therapeutic gain in a subject undergoing radiotherapy is: (1) downregulating inflammatory cytokines or reducing inflammatory cell infiltration, (2) reducing or preventing radiation-induced tissue damage, (3) increasing epithelium thickness, reducing dermis thickness, or reducing vessel density, (4) decreasing collagen deposition, (5) enhancing tumor radiosensitization, or (6) downregulating fibrogenic growth factors or preventing late radiation-induced tumorigenesis.

The Examiner pointed out in the office action dated March 23, 2007 that Samid teaches "a method for treating **cancer**ous conditions with phenylacetic acid and its pharmaceutically acceptable salts and derivatives, including sodium phenylbutyrate ... and as well, **cancer** prevention ... [; and it] also teach[es] a method of treating the **cancer**

[1] Claim 4, previously withdrawn by mistake, in fact, reads on the elected species and has now been placed under examination.

with sodium phenylbutyrate concomitantly or in combination with conventional radiotherapy." See page 4, last paragraph, lines 2-7. To facilitate discussion, Applicant will refer to phenylacetic acid, its pharmaceutically acceptable salts and derivatives below as "the Samid agents."

As also pointed out by the Examiner in yet another earlier office action dated October 1, 2007, Samid discloses that "(1) differentiation therapy is a desirable approach to **cancer** intervention since neoplastic transformation is the result of defects in cellular differentiation and thus inducing **tumor** cells to differentiate prevents **tumor** progression and brings about the reversal of malignancy ...; (2) the administration of phenylacetate and its pharmaceutically acceptable derivatives to prevent **tumor** progression and the development of malignant diseases ...; (3) a pharmaceutical composition for inhibiting abnormal cell growth and inducing differentiation in nonmalignant or malignant **tumor** cells." See page 6, last paragraph.

In the current Office Action, the Examiner further asserts that "Samid also teaches that sodium phenylacetate and its salt sodium phenyl[acetate] ... have been found to be excellent inhibitors of the growth of specific **tumor** cells, affecting the proliferation of the malignant cells while sparing normal tissues." See page 3, last paragraph, lines 1-4.

In short, the Examiner asserts that Samid teaches using the Samid agents, e.g., phenylbutyrate, as **anticancer/antitumor** agents. See column 1, lines 16-18. She concludes that "it would have been prima facie obvious to one of ordinary skill in the art to administer sodium phenylbutyrate in the manner prescribed by Samid, in combination with radiotherapy."

Applicant respectively traverses.

For the reasons discussed below, Applicant submits that claim 1, as amended, is not rendered obvious by Samid for covering the method of increasing Gains (1)-(6) in radiotherapy as recited therein and reproduced below.

Gain (1) is downregulating inflammatory cytokines or reducing inflammatory cell infiltration, i.e., preventing inflammation. Samid only teaches preventing viral infection and treating β-chain hemoglobiopathies, in addition to treating cancer/tumor. See

column 1, lines 18 and 19. As such, it does not teach or suggest using the Samid agents, e.g., phenylbutyrate, to prevent inflammation, i.e., Gain (1). Thus, as far as Gain (i) is concerned, claim 1 is not rendered obvious by Samid.

Gain (2) is reducing or preventing radiation-induced tissue damage. It is well known in the art that radiation-induced tissue damage is caused by radiation-induced persistent up-regulation of proinflammatory cytokines and fibrogenic growth factors. See the Specification, page 24, penultimate paragraph, lines 1-4. In other words, reducing or preventing radiation-induced tissue damage, i.e., Gain (2), results from phenylbutyrate-induced down-regulation of both proinflammatory cytokines and fibrogenic growth factors, shown in the Specification at pages 24-27, Examples 5-7. As mentioned above, Samid does not teach or suggest anti-inflammation, i.e., down-regulating proinflammatory cytokines. Likewise, it also does not teach or suggest downregulating fibrogenic growth factors. In short, Samid fails to teach or suggest downregulating proinflammatory cytokines or downregulating fibrogenic growth factors, or for that matter, the resultant reduction or prevention of radiation-induced tissue damage, i.e., Gain (2). Thus, as far as Gain (2) is concerned, claim 1 is not rendered obvious by Samid.

Gain (3) is increasing epithelium thickness, reducing dermis thickness, or reducing vessel density. As asserted by the Examiner above, Samid discloses that "sodium phenylacetate and its salt sodium phenyl[acetate] ... [affect] the proliferation of the malignant cells while **sparing normal tissues**." It thus teaches away from using the Samid agents, e.g., phenylbutyrate, to increase Gains (3), i.e., increasing epithelium thickness, reducing dermis thickness, or reducing vessel density, all of which requires **affecting normal tissues**. Thus, as far as Gain (3) is concerned, claim 1 is not rendered obvious by Samid.

Gain (4) is decreasing collagen deposition. Samid reveals that the Samid agents induce collagen synthesis in fibroblasts and inhibit the expression of collagenase, both of which would result in **increasing collagen deposition**. See column 11, line 51; and column 15, lines 31 and 32. As such, it teaches away from using the Samid agents, e.g.,

phenylbutyrate, to increase Gain (4), i.e., **decreasing collagen deposition**. Thus, as far as Gain (4) is concerned, claim 1 is not rendered obvious by Samid.

Gain (5) is enhancing tumor radiosensitization. It is well known in the art that enhancing tumor radiosensitization, i.e., Gain (5), increases cytotoxicity of radiation against tumor cells, which promotes **tumor cell death**. Samid, on the other hand, teaches that the Samid agents exert their antitumor effects as tumor cell differentiation inducers. See column 4, lines 44-46. In other words, it teaches that the Samid agents only induce tumor cell differentiation, **not tumor cell death**. Thus, Samid does not teach or suggest Gain (5). In other words, as far as Gain (5) is concerned, claim 1 is not rendered obvious by Samid.

Gain (6) is downregulating fibrogenic growth factors or preventing late radiation-induced tumorigenesis. It is well known in the art that the late radiation-induced tumorigenesis is caused by overexpression of fibrogenic growth factors. See the Specification, page 27, second paragraph, lines 1-4. A person skilled in the art would have expected that late radiation-induced tumorigenesis can be prevented by downregulating fibrogenic growth factor, which, as mentioned above, is not taught by Samid. In short, Samid does not teach or suggest either downregulating fibrogenic growth factors or its resultant prevention of late radiation-induced tumorigenesis, i.e., Gain (6). Thus, as far as Gain (6) is concerned, claim 1 is not rendered obvious by Samid.

As far as Gain (5) and (6) are concerned, claim 1 is also not rendered obvious on a second and independent ground.

Samid does not teach that phenylbutyrate, a hyperacetylating agent, is an antitumor agent itself. Rather, phenylbutyrate acts as **a precursor of a tumor cell differentiation inducer**, i.e., phenylacetate. See column 3, line 39. Indeed, the only reason for using phenylbutyrate in the Samid pharmaceutical formulations is that, unlike phenylacetate, phenylbutyrate is not malodorous.[2] See column 24, lines 25-29. This

[2] In the *in vitro* tumor cell differentiation experiments described in Samid, phenylacetate and its analogs, not phenylbutyrate, were used. See columns 8-17, Section A, Examples 1-11. The apparent reason to use phenylacetate and its analog, instead of phenylbutyrate, is two-fold. First, malodor of phenylacetate was

teaching in Samid would not have motivated a person skilled in the art to use histone hyperacetylating agents, especially those which cannot be readily converted to phenylacetate or its analogs, as an anti-tumor agent via inducing tumor cell differentiation, let alone as a tumor radiosensitization enhancer via increasing cytotoxicity of radiation or as a late radiation-induced tumorigenesis preventer via downregulating fibrogenic growth factors, i.e., Gain (5) or (6). For this second and independent reason, as far as Gain (5) or (6) is concerned, claim 1 is not rendered obvious by Samid.

In sum, as far as radiotherapy is concerned, claim 1, which covers a method of increasing the therapeutic gain in radiotherapy (the elected species), i.e., one of Gains (1) to (6) recited therein, is not rendered obvious by Samid.

As far as chemotherapy is concerned, claim 1, which additionally covers a method of increasing the therapeutic gain in chemotherapy (the non-elected species), i.e., Gains (1), (2), (3), **and** (4) recited therein, is also not rendered obvious by Samid. Gain (3) in chemotherapy, as recited in claim 1, is ameliorating complications or sequelae of chemotherapy, including mucositis, dermatitis, ulceration, tissue necrosis, and fibrosis. All of these conditions are caused by persistent up-regulation of proinflammatory cytokines and fibrogenic growth factors. See the Specification, page 24, penultimate paragraph, lines 1-4. As mentioned above, Samid fails to teach or suggest downregulating proinflammatory cytokines or downregulating fibrogenic growth factors, which would result in Gain (3) in chemotherapy. In short, it does not teach or suggest Gain (3) in chemotherapy. Thus, respecting chemotherapy, Samid does not render obvious claim 1, which requires Gain (3) as a part of the therapeutic gain in chemotherapy.

In view of the above remarks, Applicant respectfully submits that claim 1 is allowable over Samid. So are claims 4, 11, 14-17, 22 and 23, all of which depend from claim 1.

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irrelevant in *in vitro* studies. Second, phenylbutyrate cannot be readily converted to phenylacetate in *in vitro* systems.

CONCLUSION

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment.

In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed.

Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

The extension fee in the amount of $ 555 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 50-4189, referencing Attorney Docket No. 55701-004002.

Respectfully submitted,

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